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Editorial Comment

Unobstructed Thinking (and Terminology) Is Called for in the Understanding and Management of Hypertrophic Cardiomyopathy*

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> The ill and unfit choice of words wonderfully obstructs the understanding.
>
> —Sir Francis Bacon

> Don't just do something, stand there!
>
> —Anon.

Conventional wisdom. Conventional wisdom has accepted and promoted the primacy of obstruction in the pathophysiology of hypertrophic cardiomyopathy. The dynamic intracavitary pressure gradient, universally equated with outflow tract obstruction, is thought to be the cause of the inordinate hypertrophy of the left ventricle as well as the physical signs, symptoms and threat of premature mortality that characterize this condition. Synonyms, including idiopathic hypertrophic subaortic stenosis, muscular subaortic stenosis and hypertrophic obstructive cardiomyopathy, are widely used by physicians in their professional writings and discussions and in their characterizations and explanation of the disease to their patients.

If outflow obstruction is the cause, it logically follows that relief of obstruction should be the cure. A sphincteric contraction ring in the outflow tract was compellingly described by early surgical investigators: "forceful contraction of the outflow tract upon the examining finger is evident during systole" and "the compression around the finger was nothing short of painful"; but the presence of this sphincter could not be later confirmed by cineangiography or echocardiography. When these imaging techniques became available, they exculpated the fabled outflow tract sphincter and implicated instead anterior motion of the mitral valve leaflets (hardly capable of a painful finger squeeze!) in the presumed obstruction. Mitral valve replacement was then advocated in lieu of muscle resection when it was determined that the mitral leaflets, and not a muscular sphincter, caused the obstruction.

On the basis of observations that myocardial infarctions could abolish the pressure gradient, procedures have been devised to obstruct the nutrient arteries supplying the subaortic septum (1). Abolition of the pressure gradient has thus been the desired and most readily measured end point of all forms of therapy despite the lack of clear documentation that it has a favorable impact on the natural history of the disease.

Dual-chamber pacing is yet another arrow in the therapeutic quiver (2). The logic behind this strategy is as follows: In some patients, acute or chronic reduction or relief of the pressure gradient occurs with pacing of the right ventricle. Atrial transport function is preserved by sensing atrial depolarization, and preemptive triggering of the ventricle is induced before native conduction can take place. Attendant with pressure gradient reduction has been in some instances reduction in filling pressure, along with improvement in exercise tolerance and symptoms.

This is not truly "dual-chamber pacing" because only one chamber, the ventricle is usually paced, but the term is widely used despite its inexactitude. The terms "P-synchronous pacing" and "DDD pacing" are also used to describe the procedure, which avoids the connotation that both chambers are being paced. However, "P-synchronous pacing" is misleading because "synchronous" implies simultaneous action, rather than the advantageous sequential action of atrial sensing followed by ventricular pacing that is actually used. "DDD" obscures the modalities used, namely, "VAT" (ventricular pacing, atrial sensing, with triggering of the ventricle), or what might be more clearly described as "atrial triggered ventricular pacing."

The proposed mechanism underlying the reduction in intracavitary gradient is that pre-excitation of the apex alters the sequence of contraction of the interventricular septum such that the left ventricular outflow tract is widened (2). This concept is similar to a disputed explanation given for the mechanism of gradient reduction with ventricular myotomy and myectomy procedures, namely, the production of left bundle branch block.

The article in this issue of the Journal by Rishi et al. (3) explores the use of atrial triggered ventricular pacing (VAT pacing) in a small pediatric cohort of symptomatic patients with hypertrophic cardiomyopathy. The relevance of this test of the "obstruction (gradient) causes hypertrophy" hypothesis is especially pertinent in children because the degree of hypertrophy can advance rapidly in childhood and adolescence (2), dooming its victims to a potentially life-threatening disease. Although 6 of the 10 patients were 13 to 17 years old, and 4 of the 7 "responders" were >13 years old at the inception of the study, it could still serve as a valuable insight into the hypothesis. The decrease in pulmonary capillary wedge pressure is reassuring, although the spontaneous variability of this measurement with volume status and other factors makes it a less than solid end point when measured at one point in time.

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The modest increases in treadmill exercise time and the subjective improvement on serial quality of life questionnaires could be explained by a training effect and a placebo effect, respectively.

These latter effects can only be validly tested with randomized, double-blind, controlled studies of the type recently reported by Nishimura et al. (4) in 19 adult patients with hypertrophic cardiomyopathy. Improvement in quality of life indexes, exercise duration and maximal oxygen consumption in their sham treatment arm (implanted pacemakers programed in the AAI mode, with a backup rate of 30 beats/min) suggests a strong placebo effect of the instrumentation and a training effect on exercise performance.

Until we have more data, pacing, particularly in children, should remain experimental, and instances where it is used should be rigorously followed up and reported. Dual-chamber generators and electrodes pose special challenges in infants and small children, including the need for changing electrodes to match growth and concerns about the functional life expectancy of the devices. Some patients, including one in the current study, are subjected to radio frequency ablation of the atrioventricular node, rendering the recipient permanently pacemaker dependent. A thoracotomy for placement of epicardial leads was used in another patient in the current study, a procedure that should not be entered into lightly. Pacemakers also have a potential for causing arrhythmias, either by mechanical stimulation of the ventricular endocardium or through iatrogenic reentry phenomena. The heightened public awareness of the "painful debate" engendered by a *Wall Street Journal* article (5) and the emotional letters in response to it make it imperative that we look before we leap, particularly in regard to the use of implanted devices in children.

It is of considerable concern that recent attempts to recruit adult patients for a multicenter, prospective, randomized trial evaluating sham pacing against atrial triggered ventricular pacing have reportedly been hampered by a meager enrollment of patients. An explanation given for the lack of referral is that physicians are already convinced that pacing is a proven therapeutic modality.

The license provided an editorial comment invitee compels me to provide some other cautionary comments at this juncture. In its relatively short history since Brock (6) and Teare (7) first brought the disease into prominence, no other disease in cardiology has caused more controversy and needs more reasoned understanding than hypertrophic cardiomyopathy. At the root of the controversy are the disputes and misunderstandings regarding the dynamic intracavitary pressure gradients that underlie the condition's compelling nosology. These gradients are properly termed "dynamic" in that they respond in a manner totally unlike the gradients associated with fixed lesions such as aortic stenosis. Whether they should be equated with "outflow tract obstruction" is another matter.

Unconventional wisdom. The opening paragraphs of this editorial reiterated concepts taught to medical students and medical trainees because they are implicit in the terminology and firmly believed by our academic faculties and by the vast majority of cardiologists. These beliefs survive despite having been repeatedly challenged with observations that question the presence and importance of obstruction, as conventionally defined as a hindrance to ejection, in the pathophysiology of hypertrophic cardiomyopathy (8). A summary of these challenges as well as an alternative understanding for dynamic intracavitary gradients follows:

1. Most patients with hypertrophic cardiomyopathy do not have pressure gradients either at rest or with provocation.

2. Symptomatic patients with hypertrophic cardiomyopathy without gradients have a worse prognosis than those who do have gradients.

3. Ventricles with dynamic gradients have better systolic function than those that do not. Provocation or enhancement of a gradient is associated with an increase in the rate and degree of left ventricular emptying (the antithesis of increased obstruction, which would hinder the rate of emptying), despite the presence of systolic anterior movement of the mitral valve.

4. Dynamic pressure gradients occur in normal ventricles under a variety of perturbations that decrease left ventricular filling, decrease impedance to left ventricular ejection or increase the contractile state of the ventricle. Examples include blood loss, septic shock, pericardial tamponade and dobutamine infusion stress echocardiography.

5. Dynamic pressure gradients occur after aortic valve replacement for aortic stenosis. In a recent study, high intracavitary flow velocity signals were recorded, but systolic anterior motion of the mitral apparatus was noted in only 5 of 41 of these patients (9). One of these five patients had mitral annulus calcification, and the remaining four were noted to have elongated and redundant mitral valve architecture. It might be reasoned that these intracavitary pressure gradients could be the cause, rather than the result of systolic anterior movement. The high pressure in the submitral cavity and low pressure in the outflow tract could be the forces that bend the elongated leaflet tips and subvalvar apparatus toward the low pressure zone.

6. The mechanism underlying observations 3 to 5 has been variously called "cavity obliteration" (8), "cavity squeezing" (9) and "cavitary elimination" (10), which are clear, unambiguous descriptive terms. It occurs when there is excessive contractile force applied to the ventricle beyond that needed for ejection of the stroke volume; a mismatch between work needed and work performed. The contents of the entire submitral region of the ventricle are rapidly eliminated, with the residual "dead space" largely confined to the minimally contractile outflow region downstream from the mitral valve (8).

7. High pressures recorded from catheters entrapped in the myocardium are *not* responsible for the intracavitary gradients described in observations 3 to 6. This measurement artifact, accurately termed "catheter entrapment," does not result in Doppler velocities comparable to the pressure differences noted with cavity obliteration. Accordingly, catheter entrapment should not be equated with cavity obliteration.

Unobstructed understanding. These observations are not meant to imply that high pressure in the ventricle, whether it results from true obstruction or cavity obliteration, is benign; nor should these remarks be construed to imply that abolition of a gradient is not beneficial. The observations are being elucidated for the purpose of better understanding of the mechanism of nonobstructive dynamic gradients, in the hope that neither gradients and obstruction, nor cavity obliteration and catheter entrapment, will continue to be equated. When the terms are indiscriminately interchanged, it "wonderfully obstructs the understanding." Clear and unobstructed thinking is aided by clarity of terminology.

The stimulus to enumerate these observations is also predicated on the belief that a rush to embrace treatment modalities based on incomplete information or worse, misquoted information, is not likely to serve our patients well. The claim that septal pre-excitation widens the outflow tract (2) should be convincingly demonstrated by imaging studies before it is fully accepted as the mechanism for gradient reduction. A reduction in the rate of ventricular emptying (dV/dT) through an interruption of the sequence of contraction should be given alternative consideration.

The long-term benefits and hazards of any new technology should be judged against contemporary natural history studies. The annual mortality rate is now reported to be <1%, significantly less than in earlier decades. As the cause or causes of morbidity and mortality are better understood in hypertrophic cardiomyopathy, rational and effective therapy has and will continue to emerge. Because arrhythmias and diastolic dysfunction are now thought to be the principal causes of disability and death in hypertrophic cardiomyopathy (with or without intracavitary pressure gradients), will pacing confer benefit or hazard?

As with many conditions with familial association, future therapy may be in the realm of genetic engineering. Many of the arguments that dominate the discussions of hypertrophic cardiomyopathy today may well be irrelevant if this prediction is realized, but we can look back with nostalgia on these four decades of intellectual stimulation. Myocardial stimulation may be another matter.

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